Neuronal rac1 is required for learning-evoked neurogenesis.

Journal: J Neurosci

Publication Year: 2013

Authors: Ursula Haditsch, Matthew P Anderson, Julia Freewoman, Branden Cord, Harish Babu, Cord Brakebusch, Theo D Palmer

PubMed link: 23884931

Funding Grants: Immunology of neural stem cell fate and function

Public Summary:
There are discrete areas of the adult brain that retain stem cells and the ability to generate new neurons, a process called neurogenesis. One such region is the hippocampus, a structure that is important for learning and memory. Our goal in this study was to understand how stem cells are regulated in the healthy brain. Learning itself causes an increase in hippocampal neurogenesis and this response to circuit demand is important for hippocampal function. In this study, we examined the molecular signaling that occurs during maze learning in mice in an attempt to identify signals that stimulate stem cell activity and elevate neurogenesis. We discovered that the molecule, Rac1, operates within mature neurons to mediate the neuron's production of growth factors during learning. These growth factors stimulate an increase in stem cell activity and neurogenesis, which improves hippocampal function. We also showed that genetic elimination of Rac1 in mature neurons prevented learning-evoked neurogenesis and caused severe learning and memory deficits. These deficits could be reversed by allowing animals to exercise on a running wheel. Running is a potent stimulator of hippocampal neurogenesis and this study was able to show that exercise-induced neurogenesis is able to rescue defects in hippocampal neuron function that are reminiscent of those experienced in certain degenerative diseases, such as Alzheimer's disease. Importantly, we were also able to show that the defects in neurogenesis and learning can be pharmacologically reversed using drugs that influence neuronal function, suggesting that stimulating the brain's natural recruitment of stem cells might be effective in reducing learning and memory deficits that accompany age-related dementia.

Scientific Abstract:
Hippocampus-dependent learning and memory relies on synaptic plasticity as well as network adaptations provided by the addition of adult-born neurons. We have previously shown that activity-induced intracellular signaling through the Rho family small GTPase Rac1 is necessary in forebrain projection neurons for normal synaptic plasticity in vivo, and here we show that selective loss of neuronal Rac1 also impairs the learning-evoked increase in neurogenesis in the adult mouse hippocampus. Earlier work has indicated that experience elevates the abundance of adult-born neurons in the hippocampus primarily by enhancing the survival of neurons produced just before the learning event. Loss of Rac1 in mature projection neurons did reduce learning-evoked neurogenesis but, contrary to our expectations, these effects were not mediated by altering the survival of young neurons in the hippocampus. Instead, loss of neuronal Rac1 activation selectively impaired a learning-evoked increase in the proliferation and accumulation of neural precursors generated during the learning event itself. This indicates that experience-induced alterations in neurogenesis can be mechanistically resolved into two effects: (1) the well documented but Rac1-independent signaling cascade that enhances the survival of young postmitotic neurons; and (2) a previously unrecognized Rac1-dependent signaling cascade that stimulates the proliferative production and retention of new neurons generated during learning itself.